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Guidance for Industry

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION

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GUIDELINES FOR THE CLINICAL EVALUATION OF GASTRIC SECRETORY DEPRESSANT(GSD) DRUGS

September 1977

Comments on the contents of this publication are invited and should be addressed to the following office:

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ABSTRACT

The Food and Drug Administration, with the assistance of its scientific Advisory Committees and other outside consultants, the American Academy of Pediatrics' Committee on Drugs, and consultants to the Pharmaceutical Manufacturers' Association has developed guidelines for the clinical evaluation of new drugs. These guidelines present acceptable current approaches to the study of investigational drugs in man, and pertain to Phases I through III of the investigation. They represent generally accepted principles for arriving at valid conclusions concerning safety and effectiveness of new drugs, as well as the views of outstanding experts concerning appropriate methods of study of specific classes of drugs.

The FDA welcomes comments on the guidelines, and expects to keep them current by review and update at approximately two-year intervals.

FOREWORD

The purpose of these guidelines is to present acceptable current approaches to the study of investigational drugs in man. These guidelines contain both generalities and specifics and were developed from experience with available drugs. It is anticipated that with the passage of time these guidelines will require revision. In order to keep them current a re-review will be performed approximately every 18 to 24 months.

These guidelines are not to be interpreted as mandatory requirements by the FDA to allow continuation of clinical trials with investigational drugs or to obtain approval of a new drug for marketing. These guidelines, in part, contain recommendations for clinical studies which are recognized as desirable approaches to be used in arriving at conclusions concerning safety and effectiveness of new drugs; and in the other part they consist of the views of outstanding experts in the field as to what constitutes appropriate methods of study of specific classes of drugs. In some cases other methods may be equally applicable or newer methods may be preferable, and for certain entirely new entities it is possible that the guidelines may be only minimally applicable.

Under FDA regulations (21 CFR 10.90(b)) all clinical guidelines constitute advisory opinions on an acceptable approach to meeting regulatory requirements, and research begun in good faith under such guidelines will be accepted by the Agency for review purposes unless this guideline (or the relevant portion of it) has been formally rescinded for valid health reasons. This does not imply that results obtained in studies conducted under these guidelines will necessarily result in the approval of an application or that the studies suggested will produce the total clinical information required for approval of a particular drug.

Many of the clinical guidelines have been developed largely, or entirely, by FDA's Advisory Committees and consultants. Others were originally developed by intramural committees and consultants of FDA and of the Pharmaceutical Manufacturers Association; in these cases the guidelines were reviewed and revised, as appropriate, by FDA's Advisory Committees.

The general guidelines for the evaluation of drugs in infants and children and most of those for study of various drug classes in children were developed by the Committee on Drugs of the American Academy of Pediatrics (AAP). Some of the pediatric guidelines for specific classes were written by FDA's Advisory Committees. There was cross review and comment on the pediatric guidelines by both the Committee on Drugs of the AAP and FDA's Advisory Committees.

The Bureau of Drugs of the FDA wishes to thank the many individuals who devoted so much time and effort to the development of these guidelines.

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"General Considerations for the Clinical Evaluation of Drugs" is an important companion piece and should be reviewed prior to reading these guidelines. It contains suggestions which are applicable to investigational drug studies for most classes of drugs and enables elimination of repetitive material in each of the specific guidelines.

I. INTRODUCTION

A. Definitions

1. Gastric secretory depressant--This is defined as an agent that will depress basal or stimulated gastric secretion of HCl by 50% or more, in subjects secreting HCl at a rate of 2 meq/hr or greater, for a minimum of 30 minutes or the period for which efficacy is claimed under appropriate test conditions.

2. Gastric analysis test conditions--An appropriate gastric analysis should be performed when testing gastric secretory depressants. Gastric secretion can be measured in the basal state or after stimulation by a chemical (histamine, betazole) or hormonal (gastrin, pentagastrin) agent or by a specified test meal. The test drug should be compared to a placebo or a known effective gastric secretory depressant.

B. Classes of Gastric Secretory Depressants--There are a number of effective gastric secretory depressants including:

1. Anticholinergic agents (preganglionic and postganglionic blockers)

2. H_2 antagonists

3. Prostaglandins

4. Gastrointestinal hormones

5. Miscellaneous (peptides such as urogastrone; CNS depressants such as diazepam and chlordiazepoxide)

II. PHASE I STUDIES

A. Procedures for Documenting Mechanism of Action or Symptom Relief--If a specific mechanism of action is proposed for the gastric secretory depressant, the mechanism must be clearly stated and documented by appropriate procedures. If no mechanism of action is proposed, then this omission should be clearly stated and the relief from predefined symptoms should be documented. It is recognized that the mechanism of action of many safe and effective drugs is unknown. Nevertheless,

presentation of data to elucidate the pharmacologic effects of gastric secretory depressants should be encouraged.

If it is claimed that the gastric secretory depressant inhibits postprandial gastric secretion, appropriate studies should be done to document the effect of the test drug on gastric secretion after a meal.

If, however, it is claimed that the gastric secretory depressant under study works primarily by depressing basal or nocturnal gastric secretion, data from appropriate gastric analysis procedures must be submitted to document that the test drug does indeed have this effect.

B. **Drug Effects Other Than the Specific Effects Under Study**--In addition to suppressing HCl secretion, the test drug may have other important effects. For instance, it may have an effect on the function of the lower esophageal sphincter (especially important in patients with esophagitis), on gastric emptying (especially important in patients with gastric or duodenal ulcer), or on pepsin output; certain gastric secretory depressants may have various other effects on the central nervous system.

It is not necessary to measure all of these variables in all subjects studied in Phase I; however, it is imperative that a sufficient number of subjects be studied to provide meaningful data.

C. **Adverse Effects**--Provision should be made for reporting and, if appropriate, measuring all adverse effects. To avoid difficulties in interpreting side-effects, subjects should be excluded from Phase I studies if they have a significant history of allergy. Periodic reexamination of subjects should be performed at intervals appropriate for the drug under study. There are specific adverse effects that should be looked for with certain classes of gastric secretory depressants.

When an anticholinergic agent is being tested, the specific effects include suppression of lacrimal, salivary, and sweat gland secretion, ocular effects (particularly increased intraocular tension), and obstructive effects in the lower urinary tract. With anticholinergic agents of the ganglionic blocking type (hexamethonium salts), cardiovascular effects must be monitored carefully, particularly postural hypotension, tachycardia, and arrhythmias.

When H_2 antagonists are used, particular attention should be paid to monitoring various hematologic variables.

D. **Subjects**

1. Subjects Appropriate for Study--Women with childbearing potential (including nursing mothers) shall be excluded. The number of subjects should be adequate to provide answers valid at reasonable statistical confidence levels to the specific questions being asked. Normal, young, healthy adult males would be appropriate subjects for studying gastric secretory depressants because they usually would meet the criterion of a basal secretion rate of at least 2 meq/hr. In some instances, it might be more appropriate to use asymptomatic duodenal ulcer patients for Phase I studies. Protocols should indicate the sources from which the subjects are drawn.

2. Exclusions

   a. Duodenal ulcer that has been symptomatic within 90 days prior to entry into study

b. History of any significant gastrointestinal disease except duodenal ulcer

c. Previous complications of duodenal ulcer with the exception of perforation with simple closure

d. History of any previous gastric surgery

e. Concomitant disease or therapy

3. Description of Study Population--Accurate description of the sample studied is needed. All subjects screened by the investigator for inclusion in the study and not accepted should be recorded with the reasons for rejection. Characteristics of the study population with respect to age, sex, health status, and other relevant variables should be recorded. The number of subjects included in the Phase I study should be restricted to that necessary for obtaining the required data.

E. Pretreatment Procedures

In addition to the usual "safety" laboratory studies, laboratory studies appropriate for the drug under study, and pretreatment physical examination, the following should be performed and described:

1. Gastric Analysis--To determine if basal gastric HCl secretion meets the criterion to qualify for study.

2. Other Procedures--Fasting of subjects and other necessary preparations should be specified.

   Pretreatment workup should be performed in close proximity to the initiation of the drug study.

F. Treatment Period

1. Medication--All drugs utilized in the study, including gastric secretory stimulants, should be described and the description should include dosage, dosage forms, and other relevant data for identification.

2. Dosage--The amount per dose and the number of doses of all drugs administered should be recorded.

3. Administration--The method of administration (routes) and frequency of administration should be recorded.

4. Dose-Response--Once the safety level in single-dose studies is established, a dose-response curve may be constructed for incremental doses with sequential stepwise increases in dosage or other appropriate experimental design taking cognizance of the problem of fade.

5. Observations During Treatment--The onset of action, the pharmacologic action, and the duration of action of the drug should be recorded.

   a. Pharmacologic Action

      (1) Data on HCl concentration and HCl output will be required. Measurement of depression of stimulated gastric secretion gives results that are less variable than does measurement of depression

of basal gastric secretion. In addition, gastric secretion stimulated by a test meal provides results that are more in keeping with the clinical use of the drug.

(2) When decreases in gastric secretion are demonstrated, data should be provided that will distinguish between true gastric secretory depression and back-diffusion through a damaged or injured gastric mucosa.

b. Serum Levels of Drug

One may wish to consider studies during Phase I or Phase II which would attempt to correlate, if possible, specific blood levels with the mechanism of action of the drug or relief of symptoms.

III. PHASE II STUDIES

A. Purpose

The purpose of these studies is to determine whether symptoms or healing or both differ in patients treated with the test drug and those treated with placebo or another reference drug in one or more of the following conditions:

1. Esophagitis
2. Erosive gastritis or "stress" ulcer
3. Gastric ulcer
4. Duodenal ulcer
5. "Functional" upper gastrointestinal syndromes
6. Pancreatitis
7. Miscellaneous--Those conditions characterized by gastric acid hypersecretion (e.g., gastrinoma)
8. Other, to be specified

B. General Statements

1. Definition of Clinical Conditions--Because esophagitis, erosive gastritis, gastric ulcer, duodenal ulcer, "functional" upper gastrointestinal syndromes (idiopathic dyspepsia), and pancreatitis are all included in these guidelines, each clinical condition must meet certain specific diagnostic criteria to be included in Phase II studies. Admission to the clinical trial must be restricted to patients in whom the diagnosis is unequivocal. In some of these clinical conditions, biopsy or cytologic examination may be appropriate to exclude malignancy.

   a. Esophagitis--The diagnosis will be based on the presence of erosions or ulcers on endoscopic examination with or without documentation by endoscopic photography or another observer.

   b. Erosive gastritis including "stress ulcer." The diagnosis will be based on the presence of multiple erosions or superficial ulcers on endoscopic

examination with or without documentation by endoscopic photography or another observer.

c. Gastric ulcer--The diagnosis will be based on endoscopic or roentgenographic evidence of crater formation.

d. Duodenal ulcer--The diagnosis will be based on endoscopic or roentgenographic evidence of crater formation.

e. "Functional" upper gastrointestinal syndromes--(idiopathic dyspepsia). The diagnosis will be based on a clinical picture of symptoms referable to the upper gastrointestinal tract in the absence of significant gastrointestinal disease but with negative upper gastrointestinal radiographic studies, negative endoscopy, negative cholecystograms, and the absence of other gastrointestinal disease.

f. Pancreatitis--The diagnosis will be based on the clinical picture and clinical course (pain, antecedent history, recurrent attacks, subsequent course, etc.) and appropriate laboratory tests as well as on the exclusion of other conditions simulating pancreatitis.

g. Miscellaneous conditions--The diagnosis of clinical conditions in the miscellaneous group will be based on the demonstration of gastric acid hypersecretion as well as on specific diagnostic criteria to define the clinical entity.

2. Evidence of Effectiveness

a. Demonstration of rate and extent of mucosal healing--In patients in whom the rate and extent of healing are to be followed, these determinations may best be made by endoscopy but radiologic demonstration of an ulcer crater cannot be excluded as a valid method for these determinations. When endoscopic and radiologic techniques are used to follow rate of healing, an objective reference device (calibrated tip of biopsy forceps included in endoscopic picture or a radiopaque device of known dimension shown on roentgenogram) may be used.

b. Relief of symptoms--Partial or complete relief of previously defined specific symptoms will be evidence of effectiveness.

c. Improvement in other indices--Improvement in acceptable predefined specific indices (antacid consumption, change in size of pancreas by sonography, hospital stay, days lost from work, time of return to usual life style, morbidity, mortality, etc.) will also be accepted as evidence of effectiveness.

C. Patients

Patients with esophagitis, erosive gastritis, gastric ulcer, duodenal ulcer, idiopathic dyspepsia, pancreatitis, or miscellaneous conditions associated with gastric acid hypersecretion and who meet the diagnostic criteria as listed above are appropriate for inclusion in the clinical trial. Thus, the clinical studies will be done in specific target populations meeting specific diagnostic criteria.

The protocol should indicate the sources from which the patients are drawn.

If healing is to be assessed in esophagitis, erosive gastritis, gastric ulcer, or duodenal ulcer, an objective measuring device as described in III.B.2a should

be used. If pain is to be evaluated, there should be a compatible history for the clinical condition of at least 2 months' duration and definite pain should be present on at least 2 of the 3 days preceding the test, except for cases of pancreatitis. If pain is to be evaluated in cases of pancreatitis, pain should have been present for at least 24 hours preceding the use of the test drug.

D. Patients are to be excluded under any one of the following conditions:

1. Occurrence, within 30 days before the initiation of the drug trial, of complications that provide a compelling indication for surgical operation.

2. More than one of the clinical conditions under consideration, unless patients are equally distributed in drug and placebo groups.

3. Gastric or duodenal ulcers attributable to specific causes (e.g., gastrinoma) unless such patients are equally distributed and stratified for statistical analysis in the drug group as well as in the placebo or reference drug group.

4. Concomitant disease or therapy contraindicating trial with drug.

5. Chronic alcoholics, drug abusers, or other persons whose reliability and physical status prevent proper evaluation of a drug trial, unless this is the target population to which the therapy is directed.

Accurate description of the sample studied is needed. All subjects screened by the investigator for inclusion in the study and not accepted should be recorded with the reasons for rejection. Characteristics of the study population with respect to age, sex, health status, and any other relevant variables should be recorded.

E. Pretreatment Procedures

In addition to the usual physical examination and laboratory studies appropriate to the drug under investigation, the pretreatment workup should include procedures necessary to establish or confirm the diagnosis. It should be performed in close proximity to the initiation of the drug study.

1. Endoscopy should be performed by an experienced endoscopist (not a person in training). It is highly desirable that the same endoscopist do all of the endoscopic procedures on the same patient. Objectivity will be enhanced if a second observer records his findings independently at the same examination or if findings are documented photographically.

2. Radiologic examinations should be performed by an experienced radiologist. In addition, it is advisable for the same radiologist to do all the radiologic procedures on the same patient.

3. Gastric analysis should include basal and stimulated gastric acid secretion.

4. Other special procedures should be performed as indicated by the chemical composition of the test drug and the clinical condition under study.

F. Study Design

The randomization plans should provide for stratification of a separate protocol according to the types of clinical conditions being investigated with specific grouping of symptoms to be treated. The following should be observed:

1. The target symptoms, laboratory indices, and other special procedures to be studied should be clearly specified.

2. A double-blind stratified and randomized design of drug studied in parallel against a placebo is most desirable. A reference drug (of proven efficacy) may be appropriately used in some studies.

3. Excluded patients should be accounted for.

4. Dropouts and discontinued patients should be followed up and reported.

5. Other treatment should be applied as uniformly as possible.

6. Crossover design could be used when appropriate.

7. Appropriate statistical analyses of results as related to the original stated target symptoms and other observations should be performed.

G. Treatment Period

1. Duration of trial--The duration of the treatment period should be related to the objectives of the protocol.

2. Medication--Treatment is begun on the day after completion of the workup. Subjects are randomly assigned to the study groups. The method of random assignment should be specified in detail.

   a. Dosage

      (1) Dose schedule should be established before the study starts, and changes in dosage during the clinical trial should be avoided except when untoward effects occur.

      (2) Alternatively, different fixed dose levels may be assigned in the treatment group(s). Variation or adjustment of dosage for individual patients on the basis of symptom response alone is not encouraged.

   b. The placebo should be indistinguishable in form from the test drug and administered on the same predetermined schedule.

   c. If a reference drug is used, this also should be indistinguishable in form from the test drug and administered on the same predetermined schedule.

   d. If antacids are to be used for relief of pain (as an adjunct to the main treatment), they should be used in a uniform way throughout the study. The type of antacid should be specified. Subjects should be encouraged to used antacids rather than milk or other foods to alleviate pain. However, if milk or other food is used, this should be recorded and reported. The amount of antacid issued and the amount remaining should be recorded at each visit.

e. Other drugs--Patients should be advised not to take salicylates, analgesics, antacids (unless allowed), sedatives, stimulants, or tranquilizers. Since the patients probably will not follow this advice completely, the agents and the amounts used should be recorded. Failure to follow this advice is not grounds for exclusion from the study. Generally, in the clinical entities covered by these guidelines, with the exception of pancreatitis, prescription by the physician for medications other than antacids in addition to the drug under study should be avoided. In the case of pancreatitis, the use of analgesics or other appropriate medication is permitted. The specific drugs and amounts used should be documented.

3. Diet--No specific diet need be prescribed apart from avoidance of those foods that tend to exacerbate the symptoms. A daily diet diary is recommended.

4. Setting--Patients included in the study should be in one of the categories:

   a. Hospitalized

   b. Outpatient

   c. Fixed ratio, such as 1 week or less in the hospital and 2 weeks or more as an outpatient.

5. Observations During Treatment

   a. Toxicity--Evaluation of the toxicity of the drug under study should be carried out with appropriate observations and laboratory tests performed at specified intervals. Mechanisms for early detection of toxicity as manifested by signs, symptoms, or laboratory evidence must be built into the protocol. Specific procedures for withdrawal of the patient from the study because of toxicity should be stated in the protocol.

   b. Withdrawal of patients from trial by physician

      (1) Withdrawals will be made for reasons of toxicity or when deemed clinically appropriate because of changes in severity of illness, development of complications, or life-threatening aspects of the clinical entity being studied.

      (2) There should be preestablished criteria for withdrawals.

      (3) The reasons for withdrawals should be concisely identified.

      (4) Patients withdrawn from the study should be followed until resolution of the conditions requiring the withdrawal.

      (5) Results should be analyzed in three groups: (a) all who started on study including those who withdrew; (b) only those who completed study; and (c) only those who withdrew from study.

   c. Indices of Effectiveness--The observations required for those indices of effectiveness that have been selected for study should be carried out at specified intervals and recorded systematically during the study. These indices include, but are not restricted to, endoscopic or radiologic evaluation, gastric secretory studies, symptom analysis, antacid consumption, time lost from work, etc. Selected procedures and laboratory determinations may have to be repeated several times during the treatment period in order to detect cumulative effects of the development of tolerance.

Daily diary or evaluation sheets should be kept by the patient during the treatment period.

There should be uniform periodic visits to the physician with recorded evaluations (rating scales, etc.) until a predetermined endpoint has been reached.

H. Observations After Treatment

Appropriate follow-up observations shoud be made in order that possible delayed adverse effects are not overlooked.

I. Data Analysis

Appropriate statistical analyses of results as related to the originally stated target symptoms, laboratory tests, and special procedures should be done.

The protocol should state in advance what will be considered evidence of effectiveness, keeping in mind that statistical significance is not necessarily clinical significance. All data pertaining to indices of efficacy should be recorded on forms designed for that purpose and specified in the protocol. Diaries, symptom-rating scales, and physician and patient assessment forms should be used as appropriate. These should be pretested and shown to be workable before the study is begun.

The method of scoring each index of effectiveness should be clearly defined in the protocol. The method(s) of statistical analysis of the scores of each index of effectiveness should be clearly stated in the protocol, with literature references. (An acceptable model for a grading scale would be: 0 = none; 1 = present but patient able to carry on usual activities; 2 = interferes with usual activities; 3 = disabling.) Keeping the number of grades as few as possible facilitates the assessment.

Analysis of results should be carried out in such a way as to first include and then evaluate withdrawals; results for withdrawals alone also should be analyzed. Withdrawals include patients who withdraw from the study on their own as well as patients dropped from the study by the investigator for failure to comply with the protocol (defined here as failure to take the test drug). Patients who do take the drug but use other medications or substances or diets that are not prescribed by the protocol should be grouped separately and included.

J. Effectiveness Standards

Clinical studies should be done in specific populations that meet specific diagnostic criteria. Appropriate stratification within each specific diagnostic category should be carried out at the time of data analysis to delineate efficacy of the test drug in the setting of varying degrees of severity of the disorder. In some instances, it may be advisable to stratify patients as to age, sex, and duration of disease before randomization. In addition to data obtained pretreatment and during treatment, any preexisiting condition that might bias analysis, such as gastroesophageal reflux, should be taken into consideration in the analysis of data. Efficacy can also be shown by comparison of effects of a placebo or reference drug with those of the drug to be tested in the same patient as well as between groups of patients. Although a study design in which a patient serves as his own control may sometimes be used to demonstrate effectiveness of a new agent, if such a design is used, it is essential to allow an adequate interval between drug and placebo treatment periods so that all indices under study may return to baseline levels. The

duration of this interval will be determined by the compound being used, the clinical condition, and the indices under observation.

Two criteria must be met for a new drug to be classified as an effective gastric acid secretory depressant in specific clinical disorders: (1) the drug must be shown to decrease significantly the gastric acid secretory response under basal or stimulated conditions; (2) the drug must be shown to effect significant clinical improvement as documented by mucosal healing, relief of symptoms, or improvement in acceptable specific predefined indices.

IV. PHASE III STUDIES

This represents an extension of Phase II to include patients treated for longer periods (determined by the natural course of the clinical entity and pattern of recurrence), when appropriate, to evaluate increased risks, to detect complications, and to explore safety and effectiveness under conditions of clinical practice. In Phase III studies, it is not necessary to demonstrate depression of gastric acid secretion in patients with specific clinical entities. Appropriate indices of clinical evaluation, including physical examinations and laboratory tests, should be monitored to detect evidence of toxicity. To demonstrate additional significant evidence of effectiveness, appropriate clinical studies should be designed and performed.

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